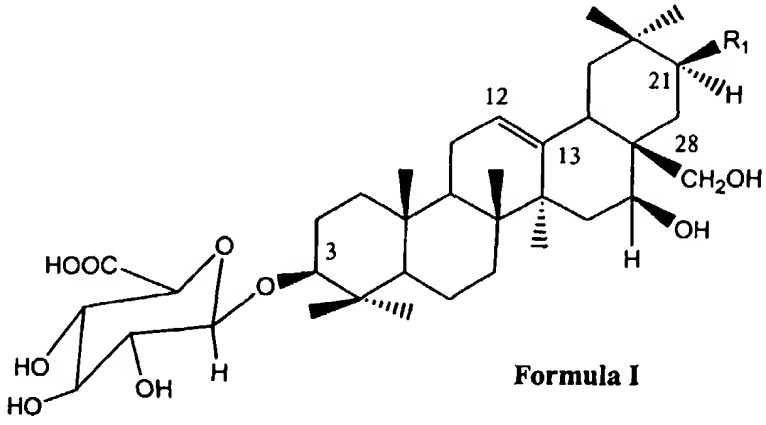
AMENDMENTS TO THE SPECIFICATION

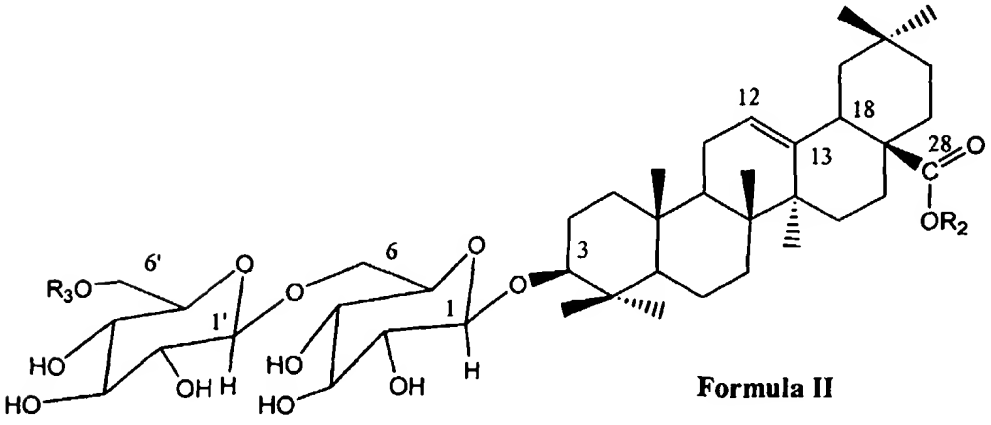
The specification has been amended as follows:

Please amend the paragraph starting at page 1, line 22, bridging page 3, line 3 (written text) as follows:

In the first part, this invention concerns Gymnemic Acid derivatives formula I or II,

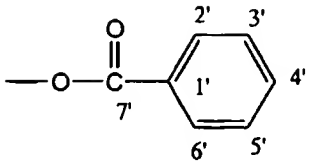


Formula I

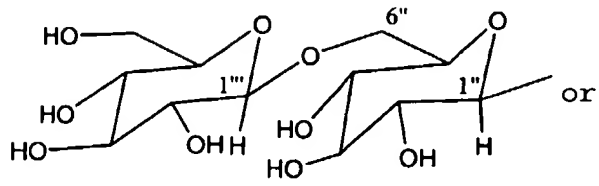


Formula II

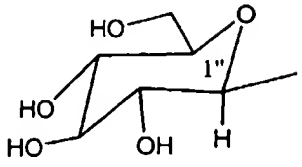
wherein, R_1 is H or the radical represented by the following formula



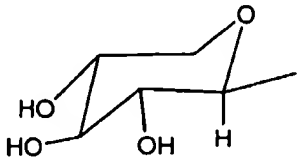
R_3 is H, and R_2 symbolizes the following radical, ~~or~~



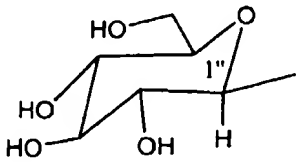
or



or R_3 symbolizes the following radical,



and R_2 is H or the following radical,



or a ~~pharmaceutically~~ pharmaceutical base addition salt thereof.

Please amend the paragraph on page 3, lines 12-17, as follows:

Another part of this invention relates to pharmaceutical composition for the prevention or treatment of the diseases associated with hyperglycemia, hyperlipidemia and platelets aggregation, which contains at least one kind of gymnemic acid derivative of formula I and/or II or pharmaceutical base addition salt thereof as ~~a~~ an active ingredient, pharmaceutical carrier and excipient.

Please amend the paragraph on page 4, lines 5-9, as follows:

Another part of this invention relates to a pharmaceutical composition for the prevention or treatment of higher blood lipid level, which contains at least one kind of gymnemic acid derivative of formula I and/or II or a pharmaceutical base addition salt thereof as an active ingredient, pharmaceutical carrier and an excipient.

Please amend the paragraph on page 4, lines 10-14, as follows:

Another part of this invention relates to pharmaceutical composition for the prevention or treatment of platelets aggregation, which contains at least one kind of gymnemic acid derivative of formula I and/or II or pharmaceutical base addition

salt thereof as an active ingredient, pharmaceutical carrier and excipient.

Please amend the paragraph beginning on page 4, line 18, bridging page 5, line 4 as follows:

a) extracting the plant Gymnema cane with ethanol under reflux and then concentrating;

b) extracting concentrated liquid in step a) with cyclohexane, then extracting with n-butanol, concentrating to dryness under reduced pressure, and then obtaining ~~an ointment~~ a paste;

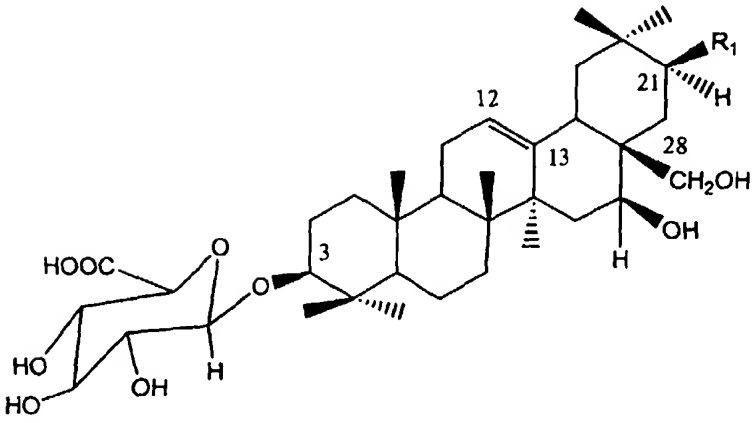
c) subjecting the ~~ointment~~ paste in step b) to silica column chromatography with ~~eluent~~ chloroform:methanol=90:10-50:5 or 90:10-60:40 (v/v) as eluant, obtaining ~~as eluent~~ gymnemic acid derivative of formula I and residue;

d) subjecting the residue in step c) to C_{18} column chromatography with ~~elute~~ methanol/water=20/80-40/60 (v/v) as eluant, obtaining ~~as eluent~~ gymnemic acid derivative of formula II;

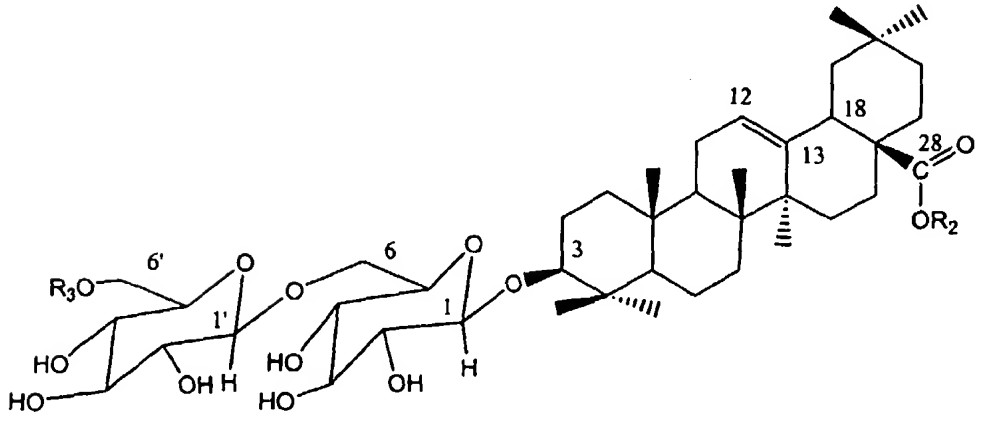
e) if desired, converting the obtained gymnemic acid derivative of formula I or II into pharmaceutical base addition salt with an inorganic or organic base.

Please amend the paragraph beginning on page 6, line 1, bridging page 7, line 4 with as follows:

This invention relates to Gymnemic Acid derivative of formula I and II,

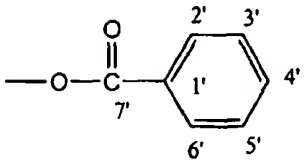


Formula I

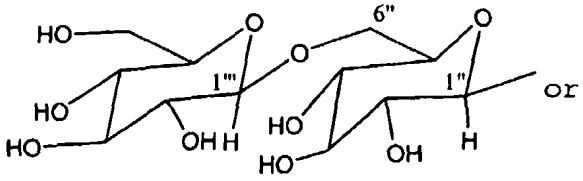


Formula II

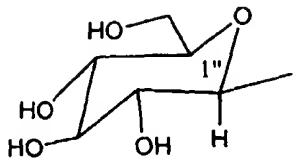
wherein, R_1 is H or the radical represented by the following formula



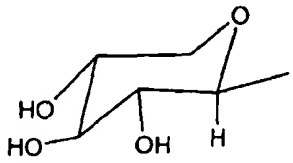
R_3 is H, and R_2 is the following group,



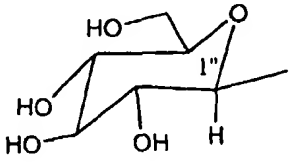
or



or R_3 is the following group,



and R_2 is H or the following group,



or the pharmaceutical base addition salt.

Please amend the paragraph beginning at page 8, line 2, as follows:

According to the invention, the Gymnemic acid compound ~~prefers~~ is preferably a Gymnemic Acid compound of formula I wherein R_1 is the following radical.

Please amend the paragraph starting at page 9, line 4, bridging page 10, line 9 as follows:

According to the invention, the pharmaceutical composition contains at least one kind of Gymnemic Acid derivative of formula I and/or II, a pharmaceutical carrier and an excipient. For example, the pharmaceutical composition may include, for example, 1.25-2.10wt% compound ~~A.~~ A, 0.89-1.50wt% compound B, 2.40-3.80wt% compound C, 2.10-3.40wt% compound D, 2.74-4.60wt% compound E, and 3.24-5.40wt% compound F (compounds A, B, C, D, E and F as defined in examples below.). This pharmaceutical composition can be administrated by gastrointestinal, parenteral or topical administration, such as oral, muscle, subcutaneous, peritonaeum, vein etc. The forms of the drug suitable for gastrointestinal administration are for example tablet, capsule, solution, suspension, powder, ~~granulate~~ granules, etc. The forms of the drug suitable for parenteral include injection solution, ~~frozen dry~~ freeze-dried powder for injection preparations, etc. The drug forms suitable for the topical use are for example, an ointment, cream, paste, patch, and spray. Of all these forms, oral administration is

preferred, and a capsule is the preferred ~~in~~ oral form. The pharmaceutical carrier or excipient of the pharmaceutical composition includes binding agent, filling material, wetting agent, disintegrating agent, surfactant, lubricating agent, diluting ~~agent~~ agent, etc. If desired, a coloring agent, flavoring agent, solubilizer, buffer, etc are also used. The diluting agents in the invention include starch, dextrin, lactose, ~~microcrystallinecellulose,~~ microcrystalline cellulose, silica gel, etc. Silica gel is preferred. The wetting agents includes water and ~~ethanol, lubricating~~ ethanol. Lubricating agents include talcum powder, and magnesium stearate.

Please amend the paragraph starting at page 10, line 21, bridging page 11, line 6 as follows:

According to this invention, the derivative or pharmaceutical base addition salt of ~~the~~ formula I Gymnemic Acid can be prepared as follows:

a) crushing dry leaves of Gymnema cane, then extracting three times with 60-95% ethanol under reflux, two hours for each, combining extracted liquid and concentrating under reduced pressure until there was no ethanol;

b) extracting the concentrated mixtures in step a) for 3 to 6 times with cyclohexane, then extracting with n-butanol,

concentrating to dryness under reduced pressure, obtaining dry extract;

c) subjecting the dry extracts in step b) to silica gel column chromatography with ~~an eluent~~ a mixture of chloroform and methanol ~~in the~~ at a ratio of 90:10 to 60:40 (v/v) as eluant, and obtaining derivatives of formula I,

d) If desired, converting the derivative of formula I in step c) into pharmaceutical base addition salt thereof.

Please amend the paragraph starting at page 11, line 7, bridging page 12, line 2 as follows:

According to this invention, the gymnemic acid derivative of formula II can be prepared as follows:

a) Crushing dry leaves of Gymnema cane, then extracting three times with 60-95% ethanol under reflux, two hours for each, combining extracted liquid and concentrating under reduced pressure until there was no ethanol;

b) extracting concentrated mixtures for 3 to 6 times with cyclohexane, then extracting with n-butanol; concentrating to dryness under reduced pressure;

c) mixing the dry extracts in step b) with ~~raw~~ rough silica gel; subjecting separation with thin layer chromatography of silica gel ~~H, the~~ H with a mixture of chloroform and methanol at a ratio

of 90:10 to 50:50 (v:v) as ~~eluent~~ eluant, subjecting the residue after elution to C_{18} column chromatography with the ~~eluent~~ eluant being methanol/water (20:80-40:60), and obtaining a derivative of formula II;

d) if desired, converting the derivative of formula II in step c) into the pharmaceutical base addition salt thereof.

Please amend the paragraph starting at page 12, lines 10-22, (not counting the formula) as follows:

~~1000g raw powder of~~ Gymnema cane leaves (1000g raw powder) were ~~refluxed~~ extracted under reflux 3 times with 60% ethanol. ~~6L of solvents~~ Six liters of solvent were used for each extraction, and ~~the extractions~~ each extraction lasted for 2 hours ~~for each time~~. The extract mixtures were combined ~~together~~ and distilled under reduced pressure until there was no ethanol, the concentrated mixture was extracted with 0.5L cyclohexane and butane for 3 times. All the n-butane extract mixtures were combined and distilled under reduced pressure to obtain 64.0g dry extract product. ~~32.0g of the~~ The dry extract (32.0g) was added into 60g of 60-100 mesh rough silica gel, and the mixture was vaporized to dryness on a water pan. 450g 200-300 mesh (m) silica gel was loaded into a column by a wet method, and then the treated sample was ~~added to be subjected to column separation with elution by 90:10 60:40 mixtures of~~

~~chloroform-methanol.~~ added. Column separation was performed using 90:10-60:40 (v:v) mixtures of chloroform-methanol as eluant. 80mg of compound A and 60mg of compound B were obtained.

Please amend the paragraph beginning on page 12, last line, bridging page 13, line 1 as follows:

The physical and ~~chemical~~ spectral data of compound A and compound B were ~~showed~~ as follows:

Please amend the paragraph on page 13, lines 3-10, as follows:

Amorphous powder: mp 198 - 202 °C; $[\alpha]_{20}^{D}$ +16.0° (c0.10, MeOH); IR ν_{max} 3414 (OH), 1724 (COOH), 1636 (C=C), 1458, 1380, 1054cm^{-1}; ^{1}HNMR (500MHz, ~~pyridin~~ pyridine - d5) δ0.86 (3H, s, Me), 0.95 (3H, s, Me), 1.01 (9H, s, 3x Me), 1.32 (3H, s, Me), 1.39 (3H, s, Me), 3.39 (1H, dd, J=4.3 and 11.8Hz, H - 3α), 3.68 (1H, d, J=10.5Hz, H - 28a), 4.43 (1H, d, J=10.5Hz, H - 28b), 4.68 (1H, m, H - 16α), 5.04 (1H, d, J=7.8Hz, H - 1 of ~~gluconic~~ glucouronic acid), 5.26 (1H, brs, H - 12); ^{13}CNMR (125MHz, ~~pyridin~~ pyridine - d5), See ~~table~~ Tables 1 and 2; FAB MS m/z 657 $[M+Na]^{+}$.

Please amend the paragraph on page 13, lines 12-21, as follows:

Amorphous; mp192 - 195 °C; $[\alpha]_{20}^{D}$ +27.2° (c 0.15, MeOH);

IR ν_{max} 3444 (OH), 1724, 1700, 1635 (C=C), 1457, 1388, 1280, 1074, 720cm^{-1}; ^{1}HNMR (500MHz, ~~pyridin~~ pyridine) δ 0.98 (3H, s, Me), 1.01 (3H, s, Me), 1.02 (9H, s, 3 x Me), 1.07 (3H, s, Me), 1.30 (3H, s, Me), 1.34 (3H, s, Me), 1.36 (3H, s, Me), 3.40 (1H, dd, J=4.5 and 12.0Hz, H - 3α), 3.70 (1H, d, J=10.2Hz, H-28a), 4.42 (1H, d, J=10.2Hz, H - 28b), 4.70 (1H, m, H - 16α), 5.10 (1H, d, J=7.8Hz, H- 1 of ~~gluconic~~ glucouronic acid), 5.70 (1H, dd, J=4.7 and 12.3Hz, H - 21α), 7.47 (3H, overlap, H - 3', - 4' and - 5'), 8.25 (2H, dd, J=1.4 and 4.8Hz, H - 2' and - 6'); ^{13}CNMR (125MHz, ~~pyridin~~ pyridine - d5), See ~~table~~ Tables 1 and 2; FAB MS m/z 777 $[M+Na]^{+}$.

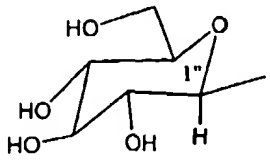
Please amend the Table 2 at page 15 as follows:

Table 2: ^{13}CNMR data of saccharide part compound A and B

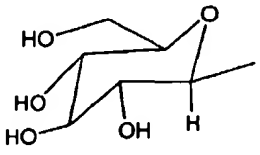
3-position substitution	Compound A	Compound B
~~Glutamic~~ Glucouronic acid 1	107.3	107.3
~~Glutamic~~ Glucouronic acid 2	75.6	75.6
~~Glutamic~~ Glucouronic acid 3	78.2	78.2
~~Glutamic~~ Glucouronic acid 4	73.5	73.6
~~Glutamic~~ Glucouronic acid 5	77.8	77.7
~~Glutamic~~ Glucouronic acid 6	173.1	173.3

Please amend the paragraph starting at page 15, line 4, as follows:

Preparation of Compound C (formula II Gymnemic Acid derivative with R_3 as H and R_2 as ~~follow~~ the following group),

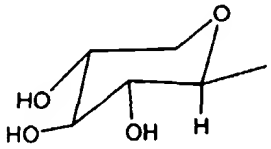


compound D (formula II Gymnemic Acid derivative with R_3 as follows and R_2 as H),

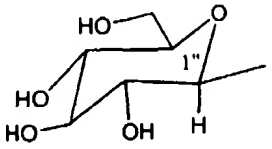


compound E(formula II Gymnemic Acid derivative with R_3 as ~~follow~~ follows),

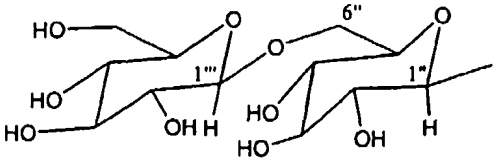
R_2 is



R_3 is



R_2 as ~~follow~~ follows and compound F(formula II Gymnemic Acid derivative with R_3 as H and R_2 as ~~follow~~ follows)



Please amend page 16, lines 6-27 as follows:

The physical and ~~chemical~~ spectral data of compound C were ~~shown~~ as follows:

Amorphous powder; mp206 - 209 °C; [α] $_{20}^{D}$ - 16.0 ° (c 0.11, MeOH); IR ν_{max} 3424 (OH), 1735 (COOR), 1636 (C=C), 1457, 1034cm^{-1}; ^{1}HNMR (400MHz, ~~pyridin~~ pyridine - d5) δ 0.82 (3H, s, Me), 0.87 (3H, s, Me), 0.91 (3H, s, Me), 0.97 (3H, s, Me), 1.07 (3H, s, Me), 1.20 (3H, s, Me), 1.23 (3H, s, Me), 3.17 (1H, dd, J=3.5 and 10.2Hz, H - 18), 3.30 (1H, d, J=3.9 and 11.7Hz, H - 3α), 5.37 (1H, brs, H - 12), ^{13}CNMR (100MHz, ~~pyridin~~ pyridine - d5), See ~~table~~ Tables 3 and 4; FAB MS m/z 943[M+H]$^{+}$.

The physical and ~~chemical~~ spectral data of compound D were ~~shown~~ as follows:

Amorphous powder; mp 202 - 204 °C ; [α]$_{20}^{D}$ - 3.2° (c 0.15, MeOH); IR ν_{max} 3410 (OH), 1710 (COOR), 1638 (C=C), 1458, 1036cm^{-1}; ^{1}HNMR (400MHz, ~~pyridin~~ pyridine - d5) δ 0.87 (3H, s, Me), 0.91 (3H, s, Me), 0.96 (3H, s, Me), 1.02 (3H, s, Me), 1.10 (3H, s, Me), 1.24 (3H, s, Me), 1.29 (3H, s, Me), 3.30 (1H, dd, J=4.5 and 11.5Hz, H - 3α), 5.38 (1H, brs, H - 12), ^{13}CNMR (100MHz, ~~pyridin~~ pyridine - d5), See ~~table~~ Tables 3 and 4; FAB MS m/z 935[M+Na]$^{+}$.

The physical and ~~chemical~~ spectral data of compound E were ~~shown~~ as follows:

Amorphous powder; mp212 - 215 °C; [α]20 - 9.6 ° (c 0.20, MeOH); IR ν_{max} 3414 (OH), 1740 (COOR), 1636 (C=C), 1460, 1364, 1044, 896cm^{-1}; ^{1}HNMR (500MHz, ~~pyridin~~ pyridine - d5) δ 0.85 (3H, s, Me), 0.90 (3H, s, Me), 0.94 (3H, s, Me), 1.00(3H, s, Me), 3.19 (1H, dd, J=4.0 and 13.7Hz, H - 18), 3.32(1H, d, J=4.4 and 11.7Hz, H - 3 α), 5.40(1H, brs, H - 12), ^{13}CNMR (100MHz, ~~pyridin~~ pyridine - d5), ~~See table~~ see Tables 3 and 4; FAB MS m/z 943 [M+Na]$^{+}$.

Please amend the paragraph starting at page 17, line 1, as follows:

The physical and ~~chemical~~ spectral data of compound F were ~~shown~~ as follows:

Amorphous powder; mp209 - 211 °C ; [α]20 - 12.1° (c 0.12, MeOH); IR ν_{max} 3424 (OH), 1734 (COOR), 1636 (C=C), 1458, 1047cm^{-1}; ^{1}HNMR (400MHz, ~~pyridin~~ pyridine - d5) δ 0.87 (3H, s, Me), 0.90 (3H, s, Me), 0.92 (3H, s, Me), 1.00 (3H, s, Me), 1.09 (3H, s, Me), 1.22 (3H, s, Me), 1.26 (3H, s, Me), 3.20 (1H, dd, J=3.5 and 13.6Hz, H - 18), 3.33(1H, d, J=4.4 and 11.5Hz, H - 3 α), 5.39 (1H, brs, H-12), ^{13}CNMR (100MHz, ~~pyridin~~ pyridine - d5), ~~See table~~ see Tables 3 and 4; FAB MS m/z 1127[M+H]$^{+}$.

Please amend the paragraph starting at page 20, line 10, as follows:

The result was, after the rats were given saccharose for 30, 60 minutes, the value of blood sugar increased apparently. The compound B at 200mg/kg and phenformin at 100mg/kg within 30 minutes can both reduce the increased value of blood sugar remarkably, and the strength of the two compounds was similar. See ~~table~~ Table 5 for the results.

Please amend the paragraph starting at page 21, line 17, as follows:

The results show that 10 days after rats were given forage having high grease, the contents of TG and cholesterol increased. Compound B 50, 100, 200mg/kg and clofibrate 100mg/kg can both reduced the contents of TG and cholesterol in blood serum of hyperlipidemia rats, and compound B 200mg/kg has the same effect as 100mg/kg clofibrate in reducing hyperlipidemia, see ~~table~~ Table 6.

Please amend the paragraph starting at page 23, line 17 as follows:

30 minutes after mice orally took dextrose, the blood sugar obviously rises. Both the compound F 100, 200mg/kg and 50mg/kg inhibits blood sugar in mice from rising. The function of the compound B 200mg/kg and glybenclamide 500mg/kg in lowering blood sugar is similar, which may be seen in ~~table~~ Table 8.

Please amend the paragraph starting at page 25, line 6, as follows:

The content of TG and cholesterol in the blood serum of rat elevates obviously after given high-fat feedstuff for 10 days. 50mg/kg, 100mg/kg, 200mg/kg of compound F and 200mg/kg clofibrate make the level of triglycerides and cholesterol in blood serum of rat with high-fat blood diseases lower. The action 200mg/kg of the compound F is the similar as to that of 100mg/kg of clofibrate in the function of lowering blood fat. (~~table~~ Table 9)

Please amend the paragraph starting at page 27, line 4, as follows:

Compound B 50, 100, 200mg/kg by continuous administration for 14 days has no obvious effect on blood sugar of normal mice, but tolbutol starting from day 3 of administration ~~show~~ shows an obvious effect for lowering the blood sugar of normal mice. The result is also seen in ~~table~~ Table 11.